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# The first synthesis of 8-aza-2-polyfluoroalkylchromones

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**Abstract**

The condensation of 3-acetyl-4,6-dimethyl-2-pyridone with $R_FCO_2Et$ in the presence of LiH in dioxane affords corresponding $R_F$-containing β-diketones, whose dehydration under the action of conc. $H_2SO_4$ gives 8-aza-5,7-dimethyl-2-polyfluoroalkylchromones.


*Keywords:* Condensation; 3-Acetyl-4,6-dimethyl-2-pyridone; $R_F$-containing β-diketones; 8-Aza-2-polyfluoroalkylchromones

## 1. Introduction

Derivatives of 8-azachromone (4*H*-pyrano[2,3-*b*]pyridin-4-one) (**1a–d**) were first synthesized in 1967 from 3-acetyl-4,6-dimethyl-2-pyridone (**2**) by Claisen condensation with corresponding esters, followed by cyclization in ethanolic HCl of the resulting diketone [1]. Further, it was shown that compounds **1b** and **e** can be obtained by the Baker-Venkataraman rearrangement of esters prepared from pyridone **2** and benzoyl or 3,4,5-trimethoxybenzoyl chlorides [2]. Zagorevskii and co-workers [3] reported that the condensation of methyl 2-(benzyloxy)nicotinate with acetonitrile afforded 2-amino-8-azachromone (**1f**), from which azachromones **1g** and **h** were also obtained [4] (Fig. 1).

Polyfluoroalkyl groups, especially the $CF_3$ group, are highly important substituents in the field of organic chemistry. The introduction of these groups into organic molecules can bring about some remarkable changes in their physical, chemical, and biological properties [5,6]. In particular, the insertion of polyfluoroalkyl substituents into 2-position of chromones activates molecules of these compounds and reveals significant differences in the reactivity of 2-alkyl- and 2-polyfluoroalkylchromones with respect to nucleophilic reagents [7,8]. Because *N*-nucleophiles react, as a rule, with chromones at the C(2) atom with pyrone ring-opening, it is reasonable to consider that 8-aza-2-polyfluoroalkylchromones will be more reactive compounds than 8-azachromones and 2-polyfluoroalkylchromones owing to a higher electrophilicity of the C(2) atom and the better leaving group ability of a 2-pyridone moiety.

## 2. Results and discussion

As part of our continuing study on the synthesis and reactivity of $R_F$-containing pyrones [9,10] and chromones [11,12], we now report our results on the preparation of 8-aza-2-polyfluoroalkylchromone by Claisen condensation of pyridone **2** with $R_FCO_2Et$. This reaction, in the presence of LiH and upon refluxing in dioxane for 0.5–3 h, afforded diketones **3a–c** with 2-pyridone moiety in 72–90% yields (2-pyridone is the predominant species in a tautomeric equilibrium with 2-hydroxypyridine [1,13]). Treatment of compounds **3a–c** with concentrated $H_2SO_4$ at ~20 °C for 5 h gave 8-aza-2-polyfluoroalkylchromones **4a–c** in high isolated yields (Scheme 1). Note that ring-chain tautomerism is observed in solutions of compounds **3a–c**. The $^1H$ and $^{19}F$ NMR spectra of **3a–c** in DMSO-$d_6$ showed two sets of signals which were consistent with the ketoenol **A** and chromanone **B** forms with the latter predominating for **3a** and **b** (90 and 85%, respectively). Changing the $R_F$ substituents from $CF_3$ and $CF_2H$ to $(CF_2)_2H$ (**3c**) is accompanied by an increase in a molar ratio of open form **A** (67%) reflecting the smaller capability of $(CF_2)_2H$ group to stabilize the cyclic hemiketal form **B**. Diketone **3a** was found to exist as a tautomeric mixture of the forms **A** and **B** in both DMSO-$d_6$ and $CDCl_3$; in the latter solvent ketoenol form **A** predominates (55%). In the crystalline state, these compounds exist in open form **A** as evidenced by their IR spectra recorded in Nujol mulls: the band of the OH group of the hemiketal at 3200–3400 $cm^{-1}$ and the band of the non-conjugated C=O group at 1700–1720 $cm^{-1}$ are absent. The IR spectra of **3a–c** showed absorption bands in the two ranges normally associated with the amide C=O group of the 2-pyridone ring at 1650–1660 $cm^{-1}$ and the ketoenol bands

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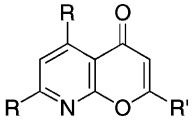



**1a-h**

R = Me, R' = Me (**a**), Ph (**b**), $CO_2Et$ (**c**),
$CO_2H$ (**d**), 3,4,5-$(MeO)_3C_6H_2$ (**e**);
R = H, R' = $NH_2$ (**f**), NHAc (**g**), $NHCO_2Et$ (**h**)

Fig. 1.

at 1615–1630 $cm^{-1}$. A weak band at 1520–1530 $cm^{-1}$ is present in the spectra of **3a–c**, and is probably due to skeletal C=C stretching [1].

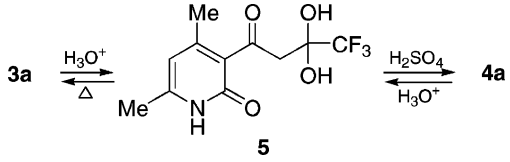
It is of interest that when compounds **3a** or **4a** are heated in aqueous acetic acid in the presence of conc. HCl for 2 h, covalent hydrate **5** is precipitated from a solution as colorless needles. Water is lost during the crystallization of hydrate **5** from toluene and diketone **3a** is formed; treatment of **5** with conc. $H_2SO_4$ at ~20 °C gives azachromone **4a** (Scheme 2). It should be noted that pyrone ring of 5,7-dimethyl-2-trifluoromethylchromone cannot add water at the activated C=C bond under the same conditions. This clearly indicates that the C(2) atom of 8-aza-2-$R_F$-chromones is more susceptible to nucleophilic attack than the corresponding atom of 2-$R_F$-chromones and makes compounds **4** attractive building blocks for the synthesis of various heterocyclic systems containing the $R_F$ group and 2-pyridone ring.

## 3. Conclusion

The reaction of pyridone **2** with fluorinated esters provides a simple and convenient process from the readily available material to 8-aza-2-polyfluoroalkylchromones **4**, which may be considered as a new $R_F$-containing substrates for the synthesis of a wide variety of heterocycles with potential biological activity.

## 4. Experimental

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400.13 and 100.62 MHz, respectively. $^{19}F$ NMR spectra were obtained on a Tesla BS-587A instrument with a working frequency of




Scheme 2.

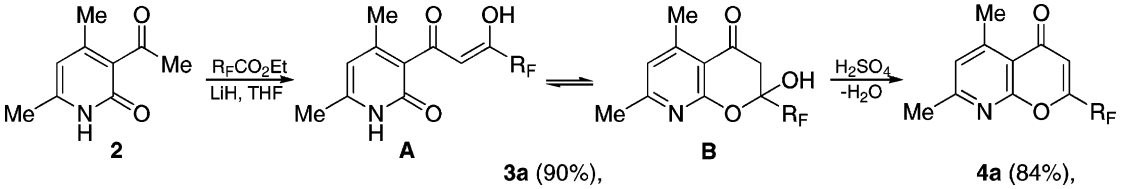
75.3 MHz. TMS was used as the internal standard for $^1H$ and $^{13}C$ NMR spectra, and $CFCl_3$ served as internal standard for $^{19}F$ NMR. The IR spectra were measured on an IKS-29 instrument as suspensions in Nujol. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting 3-acetyl-4,6-dimethyl-2-pyridone **2** was prepared by reaction of acetoacetamide with acetylacetone according to described procedure [1].

### 4.1. Typical procedure for preparation of diketones *3a–c*

Anhydrous dioxane (40 ml), pyridone **2** (3.9 g, 0.025 mol), $R_FCO_2Et$ (0.035 mol), and finely dispersed LiH (0.60 g, 0.075 mol) were placed in a round-bottom three-neck flask equipped with a mechanical stirrer and a reflux condenser. The reaction mixture was refluxed with stirring for 0.5 h for **3a**, **3c**, or 3 h for **3b** and concentrated to dryness on a water bath under reduced pressure. The residue was treated with an aqueous solution of AcOH (8 ml of AcOH, 50 ml of $H_2O$ and 100 g of ice). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from toluene as golden crystals.

### 4.2. 1-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-4,4,4-trifluorobutane-1,3-dione (*3a*)

Yield 90%, mp 195–196 °C. IR: *ν* 3165 (=CH), 1660 (C=O), 1620, 1525w (C=O, C=C) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): *δ* **A** (55%) 2.36 (s, 3H, $Me^4$), 2.46 (s, 3H, $Me^6$), 6.10 (s, 1H, $H^5$), 6.99 (s, 1H, =CH), 12.9–13.9 (br s, 1H, NH), 14.8 (br s, 1H, OH enolic); **B** (35%) 2.41 (s, 3H, $Me^7$), 2.63 (s, 3H, $Me^5$), 3.22 (s, 2H, $CH_2$), 6.71 (s, 1H, $H^6$); **5** (10%) 2.37 (s, 3H, $Me^4$), 2.41 (s, 3H, $Me^6$), 3.37 (s, 2H, $CH_2$), 6.24 (s, 1H, $H^5$), 6.59 (br s, 2H, 2OH), 12.9 (br s, 1H, NH). $^1H$ NMR (400 MHz, DMSO-$d_6$): *δ* **A** (10%) 2.21 (s, 3H, $Me^4$), 2.26 (s, 3H, $Me^6$), 6.09 (s, 1H, $H^5$), 6.72 (s, 1H, =CH), 12.1–12.4 (br s, 1H, NH); **B** (90%) 2.41 (s, 3H, $Me^7$), 2.57 (s, 3H, $Me^5$), 2.80 (d, 1H, CHH, $J_{AB}$ = 15.9 Hz), 3.41




**3a** (90%),
**3b** (72%),
**3c** (85%)

$R_F$ = $CF_3$ (**a**), $CF_2H$ (**b**), $(CF_2)_2H$ (**c**)

**4a** (84%),
**4b** (69%),
**4c** (87%)

Scheme 1.

(dd, 1H, CHH, $J_{AB}$ = 15.9 Hz, $^4J_{H,OH}$ = 1.1 Hz), 7.01 (s, 1H, $H^6$), 8.81 (d, 1H, OH, $^4J_{H,OH}$ = 1.4 Hz). $^{19}$F NMR (75.3 MHz, DMSO-$d_6$): δ **A** (8%) −75.5 (s, $CF_3$); **B** (92%) −84.5 (s, $CF_3$). Anal. Calcd. for $C_{11}H_{10}F_3NO_3$: C, 50.58; H, 3.86; N, 5.36. Found: C, 50.77; H, 3.84; N, 5.38.

### 4.3. 1-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-4,4-difluorobutane-1,3-dione (**3b**)

Yield 72%, mp 200–202 °C. IR: ν 1660 (C=O), 1630, 1530w (C=O, C=C) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ **A** (15%) 2.20 (s, 3H, $Me^4$), 2.27 (s, 3H, $Me^6$), 6.07 (s, 1H, $H^5$), 6.65 (s, 1H, =CH), 12.1–12.3 (br s, 1H, NH); **B** (85%) 2.39 (s, 3H, $Me^7$), 2.55 (s, 3H, $Me^5$), 2.64 (d, 1H, CHH, $J_{AB}$ = 16.0 Hz), 3.23 (dd, 1H, CHH, $J_{AB}$ = 16.0 Hz, $^4J_{H,OH}$ = 1.5 Hz), 6.14 (t, 1H, $HCF_2$, $^2J_{H,F}$ = 54.6 Hz), 6.95 (s, 1H, $H^6$), 8.08 (d, 1H, OH, $^4J_{H,OH}$ = 2.0 Hz). $^{19}$F NMR (75.3 MHz, DMSO-$d_6$): δ **A** (15%) −126.7 (d, $CF_2$, $^2J_{F,H}$ = 54.3 Hz); **B** (85%) −133.8 (the AB part of the ABX system, $CF_2$, $^2J_{F,F}$ = 283.2 Hz, $^2J_{F,H}$ = 54.3, 54.9 Hz). Anal. Calcd. for $C_{11}H_{11}F_2NO_3$: C, 54.32; H, 4.56; N, 5.76. Found: C, 54.52; H, 4.51; N, 5.81.

### 4.4. 1-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-4,4,5,5-tetrafluoropentane-1,3-dione (**3c**)

Yield 85%, mp 169–170 °C. IR: ν 1650 (C=O), 1615, 1520w (C=O, C=C) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ **A** (67%) 2.21 (s, 3H, $Me^4$), 2.28 (s, 3H, $Me^6$), 6.10 (s, 1H, $H^5$), 6.78 (tt, 1H, $HCF_2CF_2$, $^2J_{H,F}$ = 51.5 Hz, $^3J_{H,F}$ = 5.2 Hz), 6.80 (s, 1H, =CH), 12.1–12.3 (br s, 1H, NH); **B** (33%) 2.41 (s, 3H, $Me^7$), 2.57 (s, 3H, $Me^5$), 2.78 (d, 1H, CHH, $J_{AB}$ = 16.0 Hz), 3.35 (d, 1H, CHH, $J_{AB}$ = 16.0 Hz), 6.74 (tt, 1H, $HCF_2CF_2$, $^2J_{H,F}$ = 51.5 Hz, $^3J_{H,F}$ = 6.7 Hz), 6.99 (s, 1H, $H^6$), 8.64 (s, 1H, OH). $^{19}$F NMR (75.3 MHz, DMSO-$d_6$): δ **A** (70%) −124.9 (m, $CF_2$), −138.6 (dm, $CF_2H$, $^2J_{F,H}$ = 51.9 Hz); **B** (30%) −131.4 (m, $CF_2$), −136.6 (dm, $CF_2H$, $^2J_{F,H}$ = 51.0 Hz). Anal. Calcd. for $C_{12}H_{11}F_4NO_3$: C, 49.16; H, 3.78; N, 4.78. Found: C, 49.10; H, 3.81; N, 4.82.

### 4.5. Typical procedure for preparation of 8-azachromones **4a–c**

Diketone **3** (0.012 mol) was added to conc. $H_2SO_4$ (6 ml) and the mixture was left for 0.5 h at ~20 °C. Then the dark reaction mixture was poured into a mixture of $H_2O$ (50 ml) and ice (100 g) and the resulting crystalline product was filtered off, washed with $H_2O$, dried, and recrystallized from ethanol as a colorless crystals.

### 4.6. 5,7-Dimethyl-2-trifluoromethyl-4H-pyrano[2,3-b]pyridin-4-one (**4a**)

Yield 84%, mp 123–124 °C. IR: ν 3080 (=CH), 1675 (C=O), 1660, 1640, 1610, 1550 (C=C, Ar) $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H, $Me^7$), 2.84 (d, 3H, $Me^5$, $^4J_{H,Me}$ = 0.8 Hz), 6.67 (s, 1H, $H^3$), 7.12 (s, 1H, $H^6$). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.54 (d, 3H, $Me^7$, $^4J_{H,Me}$ = 0.4 Hz), 2.73 (d, 3H, $Me^5$, $^4J_{H,Me}$ = 0.8 Hz), 6.97 (s, 1H, $H^3$), 7.36 (s, 1H, $H^6$). $^{19}$F NMR (75.3 MHz, $CDCl_3$): δ −72.8 (s, $CF_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 22.04 (qd, $Me^5$, $^1J_{C,H}$ = 129.8 Hz, $^3J_{C,H(6)}$ = 5.0 Hz), 24.58 (qd, $Me^7$, $^1J_{C,H}$ = 128.1 Hz, $^3J_{C,H(6)}$ = 2.4 Hz), 112.11 (qd, $C^3$, $^1J_{C,H}$ = 173.7 Hz, $^3J_{C,F}$ = 2.7 Hz), 115.41 (quint., $C^{4a}$, $^3J_{C,H}$ = 3.3 Hz), 118.56 (qd, $CF_3$, $^1J_{C,F}$ = 274.1 Hz, $^3J_{C,H(3)}$ = 3.4 Hz), 125.78 (dm, $C^6$, $^1J_{C,H}$ = 163.5 Hz), 151.16 (qd, $C^2$, $^2J_{C,F}$ = 39.5 Hz, $^2J_{C,H(3)}$ = 4.3 Hz), 153.74 (qt, $C^5$, $^2J_{C,Me}$ = 6.2 Hz, $^2J_{C,H(6)}$ = $^4J_{C,H(3)}$ = 1.1 Hz), 160.70 (s, $C^{8a}$), 163.66 (qd, $C^7$, $^2J_{C,Me}$ = 6.3 Hz, $^2J_{C,H(6)}$ = 3.2 Hz), 179.07 (d, $C^4$, $^2J_{C,H(3)}$ = 1.2 Hz). Anal. Calcd. for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.27; H, 3.40; N, 5.84.

### 4.7. 2-Difluoromethyl-5,7-dimethyl-4H-pyrano[2,3-b]pyridin-4-one (**4b**)

Yield 69%, mp 136–138 °C. IR: ν 1675 (C=O), 1640, 1605, 1550 (C=C, Ar) $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H, $Me^7$), 2.84 (d, 3H, $Me^5$, $^4J_{H,Me}$ = 0.8 Hz), 6.46 (t, 1H, $HCF_2$, $^2J_{H,F}$ = 53.8 Hz), 6.56 (s, 1H, $H^3$), 7.09 (s, 1H, $H^6$). $^{19}$F NMR (75.3 MHz, $CDCl_3$): δ −125.0 (d, $CF_2$, $^2J_{F,H}$ = 53.7 Hz). Anal. Calcd. for $C_{11}H_9F_2NO_2$: C, 58.67; H, 4.03; N, 6.22. Found: C, 58.73; H, 4.04; N, 6.24.

### 4.8. 5,7-Dimethyl-2-(1,1,2,2-tetrafluoroethyl)-4H-pyrano[2,3-b]pyridin-4-one (**4c**)

Yield 87%, mp 129–130 °C. IR: ν 1670 (C=O), 1650, 1610, 1550 (C=C, Ar) $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.62 (s, 3H, $Me^7$), 2.85 (d, 3H, $Me^5$, $^4J_{H,Me}$ = 0.7 Hz), 6.23 (tt, 1H, $HCF_2CF_2$, $^2J_{H,F}$ = 52.9 Hz, $^3J_{H,F}$ = 4.2 Hz), 6.69 (s, 1H, $H^3$), 7.11 (s, 1H, $H^6$). $^{19}$F NMR (75.3 MHz, $CDCl_3$): δ −123.6 (dt, $CF_2$, $^3J_{F,F}$ = 6.1 Hz, $^3J_{F,H}$ = 4.3 Hz), −137.7 (dt, $CF_2H$, $^2J_{F,H}$ = 52.9 Hz, $^3J_{F,F}$ = 6.1 Hz). Anal. Calcd. for $C_{12}H_9F_4NO_2$: C, 52.37; H, 3.30; N, 5.09. Found: C, 52.46; H, 3.49; N, 5.04.

### 4.9. 4,6-Dimethyl-3-(4,4,4-trifluoro-3,3-dihydroxybutyryl)-1H-pyridin-2-one (**5**)

A mixture of azachromone **4a** (0.24 g, 0.99 mmol), AcOH (2 ml), conc. HCl (0.3 ml), and $H_2O$ (0.5 ml) was heated for 2 h and then left for 3 days at room temperature. The resulting colorless crystals were filtered off and dried; yield 0.16 g (58%), mp 199–202 °C. Diketone **3a** under the same conditions gave hydrate **5** in 75% yield; water is then lost during the crystallization from toluene. IR: ν 3490, 3300 (OH), 1660, 1645 (C=O), 1620, 1515 (Ar) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): δ **5** (86%) 2.15 (s, 3H, $Me^4$), 2.21 (s, 3H, $Me^6$), 3.24 (s, 2H, $CH_2$), 6.10 (s, 1H, $H^5$), 7.36 (s, 2H, 2OH), 12.15 (s, 1H,

NH) and 14% of **3a** in form **B**. $^{19}F$ NMR (75.3 MHz, DMSO-$d_6$): $\delta$ **5** (85%) −84.6 (s, $CF_3$). Anal. Calcd. for $C_{11}H_{12}F_3NO_4$: C, 47.32; H, 4.33; N, 5.02. Found: C, 47.34; H, 4.31; N, 4.84.

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